1. Process of preparing 1,2,2,2-tetrafluoroethyl-difluoromethyl ether - GBF 1989-12-06 2219292/GB-A NDN- 124-0493-0923-4

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PATENT APPLICATION NUMBER- GB8912072 GB/07 DATE FILED- 1989-05-25 PUBLICATION NUMBER- >2219292/GB-A< PUBLICATION DATE- 1989-12-06 AUTHOR/INVENTOR ADDRESS- Kawai, Toshikazu, 3-25-21 Semba-cho Kawagoe City JP PATENT ASSIGNEE(S)- Central Glass Company Limited(JP) No.5253 Oaza Okiube Ube City Yamaguchi Prefecture 755 JP ASSIGNEE ADDRESS- Central Glass Company Limited(JP) No.5253 Oaza Okiube Ube City Yamaguchi Prefecture 755 JP INTERNATIONAL PATENT CLASS- C07C04122 PATENT APPLICATION PRIORITY- 63131453 PRIORITY COUNTRY CODE- JP PRIORITY DATE- 1988-05-31

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2. PRODUCTION OF FLUORINE-CONTAINING ETHER COMPOUND - PAJ 07-01-94 06192154 JP NDN- 190-0168-2332-2

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PURPOSE: To provide a method for selectively producing a fluorine-containing ether compound through a regioselective fluorination reaction in the presence of a higher-order metal fluoride compound under a mild condition. CONSTITUTION: This method for production of a fluorine-containing ether compound represented by formula CF(sub)3(end sub)CFHOR (R is difluoromethyl or 2,2,2- trifluoroethyl) is carried out characteristically by monofluorinating the methylene position of a fluorine-containing ether compound represented by the formula CF(sub)3(end sub)CH(sub)2(end sub)OR (R is the same as in the former formula) in the presence of a higher-order metal fluoride as the fluorination agent.

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(54) Process of preparing 1,2,2,2-tetrafluoroethyl-difluoromethyl ether

(57) $CF_3CHFOCHF_2$ useful as an anaesthetic is formed by fluorinating $CF_3CHXOCHF_2$, wherein X is a halogen atom other than fluorine atom, by an alkali metal fluoride in an aprotic polar solvent in the presence of a phase-transfer catalyst such as tetramethylammonium chloride or 18-crown-6-ether. The reaction proceeds under mild conditions, and the selectivity to th aimed compound is very high. The aimed compound can easily be separated from unreacted starting compound since the boiling point of the starting compound sufficiently differs from that of the aimed compound.

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PROCESS OF PREPARING 1,2,2,2-TETRAFLUOROETHYL-DIFLUOROMETHYL ETHER

This invention relates to a process of preparing 1,2,2,2-tetrafluoroethyldifluoromethyl ether which is a compound useful as an anaesthetic.

USP 3,897,502 shows that 1,2,2,2-tetrafluoroethyl-difluoromethyl ether is obtained by fluorinating 2,2,2-trifluoroethyldifluoromethyl ether by molecular fluorine. From a practical point of view it is inconvenient to use dangerous fluorine gas, and in this fluorination reaction both the conversion of the starting compound and selectivity to the aimed compound are low. Furthermore, it is difficult to purify the reaction product by distillation because the boiling point of the starting compound is close to that of the aimed compound, and hence it is difficult to obtain the aimed compound with sufficiently high purity to use it as an anaesthetic.

DE-A 2,361,508 shows that 1,2,2,2-tetrafluoroethyl-difluoromethyl ether is obtained by fluorinating 1,2,2,2-tetrafluoroethyldichloromethyl ether by hydrofluoric acid. In practice, hydrofluoric acid too is a dangerous material. Furthermore, the principal product of this reaction is 1,2,2,2-tetrafluoroethyl-chlorofluoromethyl ether, and only a small amount of 1,2,2,2-tetrafluoroethyldifluoromethyl ether forms as a

by-product. Also in this case it is difficult to obtain 1,2,2,2-tetrafluoroethyldifluoromethyl ether of high purity.

It is an object of the present invention to provide a process of preparing 1,2,2,2-tetrafluoroethyldifluoromethyl ether of high purity at good yield by using a fluorinating agent convenient for practical use.

According to the invention there is provided a process of preparing 1,2,2,2-tetrafluoroethyldifluoromethyl ether, comprising reacting a compound represented by the general formula $CF_3CHXOCHF_2$, wherein X is a halogen atom other than fluorine atom, with an alkali metal fluoride in an aprotic polar solvent in the presence of a phase-transfer catalyst.

The fluorination reaction according to the invention is represented by the following equation.

$$CF_3CHXOCHF_2 + MF \longrightarrow CF_3CHFOCHF_2 + MX$$

wherein M represents an alkali metal.

As the starting $CF_3CHXOCHF_2$, either 1-chloro-2,2,2-trifluoroethyldifluoromethyl ether or 1-bromo-2,2,2-trifluoroethyldifluoromethyl ether is preferred.

It is a merit of this invention that an alkali metal fluoride, viz. a compound convenient for handling as an industrial material, is employed as the fluorinating agent. Moreover, the reaction between the starting compound and the fluorinating agent proceeds under mild

conditions and forms the aimed compound, 1,2,2,2-tetrafluoroethyldifluoromethyl ether, with very high selectivity and with only very small amounts of by-products attributed to side reactions, and the aimed compound can easily be purified by distillation of the reaction product containing unreacted starting compound because the boiling point of the starting compound is not close to that of the aimed compound.

In this invention the fluorinating agent is preferably selected from sodium fluoride, potassium fluoride and cesium fluoride. It is necessary to use at least one mol of an alkali metal fluoride per mol of the starting ether, $CF_3CHXOCHF_2$.

The fluorination reaction according to the invention is carried out in an aprotic polar solvent. Good examples of useful solvents are sulfolan, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, acetonitrile and hexamethylphosphoramide.

The rate of the fluorination reaction and the yield of the aimed compound are enhanced by using a phase-transfer catalyst. It is preferred to select the phase-transfer catalyst from tetramethylammonium chloride, tetra-n-butylammonium bromide, benzyltrimethylammonium chloride, benzyltriethylammonium bromide, dodecyltrimethyammonium chloride and crown ethers such as 18-crown-6-ether and dibenzo-18-crown-6-ether. A suitable

amount of the catalyst ranges from 0.01 to 10 wt% of the starting ether.

It is suitable to carry out the fluorination reaction at a temperature in the range from 30 to 300°C. When the reaction temperature is below 30°C the rate of the reaction is very low. When the reaction temperature is above 300°C considerable amounts of by-products are formed besides the aimed compound. The reaction time is variable depending on the reaction temperature and the quantity of the starting compound. In general it takes a few hours to tens of hours to complete the reaction. Usually the fluorination reaction is performed in an autoclave with continuous stirring.

The reaction according to the invention gives a mixture of the aimed compound, unreacted starting compound, alkali metal halides, inevitable by-products and solvent. It is possible to directly subject this mixture to distillation to thereby obtain $CF_3CHFOCHF_2$ of high purity. However, for easily obtaining the aimed compound of high purity usually it is better to take the steps of adding water to the mixture obtained by the reaction and allowing the resultant mixture to separate into aqueous and organic layers and then subjecting only the organic layer to distillation.

The invention is further illustrated by the following nonlimitative examples.

EXAMPLE 1

A 500-ml autoclave was charged with 300 g of sulfolan, 110 g of $CF_3CHClOCHF_2$, 52 g of potassium fluoride and 2 g of tetramethylammonium chloride, and the mixture was stirred at 210°C for 4 hr to cause the ether to react with potassium fluoride.

After the reaction the mixture containing the reaction product was mixed with 500 g of water, and the resultant mixture was allowed to separate into an organic layer and an aqueous layer. By analysis by gas chromatography, the solute of the organic layer consisted of 64.0% of unreacted $CF_3CHClOCHF_2$, 33.9% of $CF_3CHFOCHF_2$ and 2.1% of by-produced other compounds. That is, in the reaction the selectivity to $CF_3CHFOCHF_2$ was 94.2%. By distiling this organic mixture 30.7 g of $CF_3CHFOCHF_2$ of 99.9% purity was obtained.

COMPARATIVE EXAMPLE

The fluorination reaction of Example 1 was repeated except that the addition of tetramethylammonium chloride was omitted. No alternative catalyst was used.

After the reaction the mixture containing the reaction product was mixed with 500 g of water, and the resultant mixture was allowed to separate into an organic layer and an aqueous layer. By gas chromatography analysis, the solute of the organic layer consisted of 65.5% of unreacted $CF_3CHClOCHF_2$, 6.5% of $CF_3CHFOCHF_2$ and 28.0% of by-produced other compounds.

That is, in the reaction the selectivity to $CF_3CHFOCHF_2$ was 18.8%. This organic mixture was subjected to distillation, but it was impossible to obtain $CF_3CHFOCHF_2$ of sufficiently high purity.

EXAMPLE 2

A 1500-ml autoclave was charged with 600 g of N,N-dimethylformamide, 200 g of $CF_3CHClOCHF_2$, 104 g of potassium fluoride and 4.0 g of tetramethylammonium chloride, and the mixture was stirred at 220°C for 4 hr to cause the ether to react with the fluoride.

After the reaction the mixture containing the reaction product was filtered. The filtrate was analyzed by gas chromatography to find that the solute consisted of 55.2% of unreacted $CF_3CHClOCHF_2$, 42.3% of $CH_3CHFOCHF_2$ and 2.5% of by-produced other compounds. That is, in the reaction the selectivity to $CF_3CHFOCHF_2$ was 94.4%. By distilling the organic mixture 78.2 g of $CF_3CHFOCHF_2$ of 99.9% purity was obtained.

EXAMPLE 3

A 100-ml autoclave was charged with 60.0 g of sulfolan, 27.3 g of $CF_3CHBrOCHF_2$, 10.0 g of potassium fluoride and 0.5 g of tetra-n-butylammonium bromide, and the mixture was stirred at 210°C for 4 hr to cause the ether to react with the fluoride.

After the reaction the mixture containing the reaction product was mixed with 100 g of water, and the resultant mixture was allowed to separate into an

organic layer and an aqueous layer. By analysis by gas chromatography the solute of the organic layer consisted of 39.6% of unreacted $CF_3CHBrOCHF_2$, 58.6% of $CF_3CHFOCHF_2$ and 1.8% of by-produced other compounds. That is, in the reaction the selectivity to $CF_3CHFOCHF_2$ was 97.0%. The organic mixture was subjected to distillation to obtain 10.1 g of $CF_3CHFOCHF_2$ of 99.9% purity.

EXAMPLE 4

A 100-ml autoclave was charged with 60.0 g of sulfolan, 22.0 g of $CF_3CHClOCHF_2$, 20.0 g of cesium fluoride and 0.4 g of 18-crown-6-ether, and the mixture was stirred at 170°C for 4 hr to cause the halogenated ether to react with the fluoride.

After the reaction the mixture containing the reaction product was mixed with 80 g of water, and the resultant mixture was allowed to separate into an organic layer and an aqueous layer. By analysi by gas chromatography the solute of the organic layer consisted of 26.3% of unreacted $CF_3CHClOCHF_2$, 72.6% of $CF_3CHFOCHF_2$ and 1.1% of by-produced other compounds. That is, in the reaction the selectivity to $CF_3CHFOCHF_2$ was 98.5%. The organic mixture was subjected to distillation to obtain 13.0 g of $CF_3CHFOCHF_2$ of 99.9% purity.

CLAIMS

1. A process of preparing 1,2,2,2-tetrafluoroethyl-difluoromethyl ether, comprising reacting a compound represented by the general formula $CF_3CHXOCHF_2$, wherein X is a halogen atom other than fluorine atom, with an alkali metal fluoride in an aprptic polar solvent in the presence of a phase-transfer catalyst.

2. A process according to Claim 1, wherein said compound is selected from 1-chloro-2,2,2-trifluoroethyldifluoromethyl ether and 1-bromo-2,2,2-trifluoroethyldifluoromethyl ether.

3. A process according to Claim 1 or 2, wherein said alkali metal fluoride is selected from sodium fluoride, potassium fluoride and cesium fluoride.

4. A process according to Claim 1, 2 or 3, wherein said phase-transfer catalyst is selected from tetramethylammonium chloride, tetra-n-butylammonium bromide, benzyltrimethylammonium chloride, benzyl-triethylammonium bromide and dodecyltrimethylammonium chloride.

5. A process according to Claim 1, 2 or 3, wherein said phase-transfer catalyst is selected from 18-crown-6-ether and dibenzo-18-crown-6-ether.

6. A process according to any of the preceding claims, wherein the reaction is carried out at a temperature in the range from 30 to 300°C.

7. A process according to any of the preceding claims, wherein said aprotic polar solvent is selected from sulfolan, N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile and hexamethylphosphoramide.

8. A process of preparing 1,2,2,2-tetrafluoroethyl-difluoromethyl ether, substantially as hereinbefore described in any of Examples 1 to 4.